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IN THE MATTER f United States Patent Application No. 09/463082 in the name of The Australian National University

STATUTORY DECLARATION

I, Timothy John Senden, of 27 Bandjalong Crescent, Aranda, ACT 2614, Australia, do solemnly and sincerely declare as follows:

1. I am an inventor of the invention which is the subject of United States Application No. 09/463,082 (hereafter "the application") and I am well acquainted with the specification filed in respect of the application, including the invention defined in the claims of the application. Furthermore, I am acquainted with the Official Actions which have issued in respect of the application, including the Official Action dated 27 June 2002. I am also well acquainted with the documents raised as citations during examination of the application, including Burch et al (Nuc. Med. Communications), Chignier et al (Biomat.), Watson et al (WO 93/15768) and Senden et al (Journal of Nuclear Medicine).

2. It is my understanding that the Examiner has maintained objection to the claims of the application on the basis of the four documents referred to in the preceding paragraph on the basis that Burch et al discloses "Technegas" to be a carbon-based aqueous aerosol which includes Technetium-99m and the use of such aqueous aerosols for imaging of lung tissue via inhalation; that Chignier et al illustrates that carbon binds to fibrin; that Senden illustrates that Technegas contains discrete radio-labelled fullerenes; and finally that Watson illustrates carbon particles as diagnostic and therapeutic agents. I understand that the Examiner believes that the combination of these documents would lead one of ordinary skill in the art to the invention which is defined in the application. I have been asked as an inventor in respect of the invention which is the subject of the application to provide my comments on the Examiner's argument given my understanding of the invention, the application (including the claims as defined in the application) and particularly given my understanding of the citations

raised.

3. Firstly, dealing with Burch et al, I note that this document does not in fact relate to wet or aqueous aerosols. Rather, Burch et al teaches the opposite of such aerosols. In this regard, the Examiner has pointed to a brief mention of an "aqueous aerosol" on page 865, third paragraph, but has apparently failed to realise that this disclosure is in fact in relation to the prior art and is provided in Burch et al only as a means of comparison with the invention of Burch et al.

4. In Burch et al, Burch contrasts the poor efficacy of wet aerosols with his novel product in which a technetium compound is reduced at elevated temperatures. Burch et al plainly describes an aerosol produced in the *absence* of all water (see Methods section)

> "In summary, the procedure involves the evaporation to dryness of 140 MBq of sodium pertechnetate in normal saline (standard generator eluent) in a graphite crucible. The crucible is heated to 2500°C in an atmosphere of pure oxygen for 15 s. ".

5. Burch et al states that this product, upon inhalation diffuses down to "and adheres to the alveolar walls".The depth of penetration and the lack of transport across the blood-air barrier is not typical of , an ordinary wet aerosol. If this product was "wet" it would certainly cross the blood-air barrier in the lung. Further, the distinction between a true gas and Technegas is made by Burch et al. The penetration index for Technegas exceeds unity, which indicates the lack of mobility of the product (adherence) within the lung compared with the equilibrium diffusion of true gases.

6. Finally, it is my understanding from Burch et al that the aim was to illustrate a novel device for the production of "gas-like" species from suitable radio-isotopes of medical value corresponding with a clear teaching away from the use of aqueous aerosols, as clearly indicated by the comparative reference to such aerosols in Burch et al. As such, Burch et al falls well short of the teaching described by the Examiner in the

recent office action of 27 June 2002.

7. Chignier et al demonstrates the biocompatability of vitreous or glassy carbon. The emphasis of the work of Chignier et al is on the integration of this form of carbon into prosthesis. The material is described as "rough and porous" and shows short term depositions of fibrin and other blood proteins, particularly collagen. However, the work of Chignier et al focuses on the general conclusion that "at two months both arterial and intracardiac implants were free of any thrombotic deposit, the whole implant was covered macroscopically by a thin membrane." This is to state that glassy carbon does not support long term fibrin deposition. The work "emphasizes the importance of the physical properties of the material surface" which contrasts with the invention and chemical claims of the application.

8. Finally, I note that glassy carbon is not graphitic, nor fullerenic. It is half way between diamond and amorphous carbon. As such, Chignier et al does not illustrate that fibrin adheres to carbon particles in accordance with the present invention as suggested by the Examiner. I note that a chemist would not confuse the forms of carbon defined in the claims of the application with those described in Chignier et al.

9. Turning to Senden et al, the Examiner has suggested that Senden has been relied upon for teaching that Technegas contains discrete radio-labelled fullerenes. In fact, Senden et al deals with the structural and chemical elucidation of Technegas and does not address the structure of the particle described in the application directly, but rather a modified form of it. Importantly, Senden et al states that Technegas is not a fullerene.

10. Senden et al state;

> "No evidence for the presence of TcC [technetium carbide] was found in the aerosol output. Force microscopy of the surface of the technetium platelets revealed a covering with a layer of graphite. Two arguments could be used against the presence of a technetium-fullerene species. First the great bulk of technetium aerosol can be accounted for as hexagonal platelets. Second, the conditions are far from optimal for the efficient production of fullerenes."

11. In conclusion, Senden et al states emphatically that "Technegas particles are hexagonal platelets of metallic technetium, each closely encapsulated with a thin layer of graphitic carbon". The use of "graphitic" separates the structure of the carbon from that of fullerenes without ambiguity.

12. Watson et al does not specify the method of production detailed and predated by Burch et al. The work of Watson et al does not stand up against the recent and numerous applications claimed for fullerene-based drugs and so I do not believe that it can be effectively used against a non-fullerene as defined in the application. Further, the combination of Watson et al with the work of Senden et al cannot lead to the material claimed in the application. Specifically, Watson et al does not describe in any form fibrin labelling and Senden et al does not demonstrate the preparation of material for injection.

13. Still further, the combination of Burch and Chignier is equally unproductive. The Burch et al product cannot be dispersed in aqueous media, nor does it have the chemical form or physical structure of the Chignier et al carbon. The Chignier et al material is expressly for prosthetic devices and requires bio-compatibility, not the singular reaction to the blood protein, fibrin. I note that no other affinity with any other blood protein is claimed in the application.

14. Further to the above, I believe that even the full combination of the four documents cited by the Examiner does not arrive at the invention of the application. None of the citations employ the correct method of particle capture and conversion into an aqueous dispersion for administration.

AND I MAKE this solemn declaration by virtue of the Statutory Declarations Act 1959 as amended and subject to the penalties provided by that Act for the making of false statements in statutory declarations, conscientiously believing the statements contained in this declaration to be true and correct in every particular.

DECLARED at Canberra in the State of ACT
this 21st day of October, 2002

Timothy J Sander.

Before me: Cindy Bradley

31. A method for the *in vivo* detection of fibrin in a patient, said method comprising the steps of:
administering to said patient an effective amount of a detectable reagent comprising discrete particles comprising a detectable marker encased in at least two layers of carbon dispersed in a pharmaceutically or veterinarily acceptable carrier, diluent, excipient, adjuvant or any combination thereof;
binding at least some of said particles to said fibrin; and
detecting the presence of said detectable marker in said patient.

32. A method for the detection of fibrin in a liquid containing fibrin, said method comprising the steps of:
supplying to said liquid a detectable reagent comprising discrete particles comprising a detectable marker encased in at least two layers of carbon, dispersed in a carrier, diluent, excipient, adjuvant or any combination thereof;
binding at least some of said particles to said fibrin; and
detecting the presence of said detectable marker in said liquid.

41. A detectable reagent for use in *in vivo* or *in vitro* detection of fibrin, said detectable reagent comprising discrete particles comprising a detectable marker encased in at least two layers of carbon said particles preferentially binding to fibrin over other blood plasma proteins and being dispersed in a carrier, diluent, excipient, adjuvant or any combination thereof.

50. The method of targeting a drug to a localized fibrin site *in vivo*, the method comprising the steps of:
administering to a patient an effective amount of a reagent comprising discrete particles comprising at least two layers of carbon and having coupled thereto a drug to be targeted to the localized fibrin site, the particles being dispersed in a veterinarily or pharmaceutically acceptable carrier, diluent, excipient, adjuvant or any combination thereof; and
binding said particles to said localized fibrin site;
whereby said drug is targeted to said fibrin site.